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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

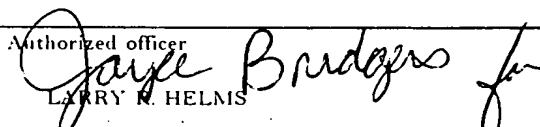
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference OCR-679B	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/16481	International filing date (day/month/year) 14 JUNE 2000	Priority date (day/month/year) 01 JULY 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant YALE UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 08 JANUARY 2001	Date of completion of this report 29 AUGUST 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer  LARRY N. HELMS Telephone No. (703) 305-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/16481

I. Basis of the report**1. With regard to the elements of the international application:***

- ☒ the international application as originally filed
- ☒ the description:
pages 1-42 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____
- ☒ the claims:
pages 43-45 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____
- ☒ the drawings:
pages 1-16 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____
- ☒ the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/16481

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)

Claims	<u>1-20</u>	YES
Claims	<u>NONE</u>	NO

Inventive Step (IS)

Claims	<u>NONE</u>	YES
Claims	<u>1-20</u>	NO

Industrial Applicability (IA)

Claims	<u>1-20</u>	YES
Claims	<u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1-20 lack an inventive step under PCT Article 33(3) as being obvious over Thorpe et al (US Patent 5,877,289, 02.03.99) in view of Berkner et al., (U.S. Patent 5,861,374, issued 19.01.99) and Wang et al (Proc. Natl. Acad. Sci. USA 96:1627-1632, 1999).

The claims are summarized as a composition comprising an immunoconjugate protein constructed as dimer of two denticle chains each with an Fc region conjugated to a mutant form of factor VII that binds but does not initiate blood coagulation. Further claimed is a serine to alanine at 344, an antibody fragment that binds a tumor cell, vectors, methods of treating with the immunoconjugate for cancer wherein the patient is administered an immunoconjugate or a adenoviral vector encoding the immunoconjugate.

Thorpe et al teach immunoconjugates comprising bispecific antibodies, scFv, and tissue factor mutants wherein factor VII is mutated such that it is not activated in the coagulation cascade (see figure 5 and column 10, lines 10-23. Thorpe et al also teach the compositions can be used for treating both benign and malignant diseases that have a vascular component, such as rheumatoid arthritis and binding to tumor cells (see column 6). Thorpe et al does not teach an alanine to serine mutant VII at position 344 or a dimer of two FC regions and a targeting moiety. these deficiencies are made up for in the teachings of Berkner et al and Wang et al.

Berkner et al teach mutant forms of factor VII at position 344 to treat a variety of disorders.

Wang et al teach an immunoconjugate comprising a dimer of the Fc region of an antibody and scFv molecules.

It would have been obvious to one skilled in the art at the time the claimed invention was made to have combined the teachings of Thorpe et al, Wang et al, and Berkner et al to produce the claimed invention.

One would have been motivated to produce the claimed invention because Thorpe et al teach the modified tissue factors may be modified to contain moieties suitable for linking the tissue factor to a second agent such as a binding region (see column 10, lines 59-64). In addition, one would have been (Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/16481

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): C07K 16/00; A61K 39/395 and US Cl.: 530/387.1, 387.3, 424/130.1, 133.1, 134.1, 135.1, 155.1

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

motivated to produce the claimed invention because Berkner et al teach mutations in the factor VII that result in reduced catalytic activation of other factors wherein the mutation is at position 344 of the catalytic triad in factor VII and it would be obvious to screen for other mutations with the same characteristics. Moreover, one would have been motivated to produce the claimed invention because Wang et al teach "the preliminary evidence that immunoconjugates could have a potential role in immunotherapy protocols with melanoma and other cancers for which tumor-specific scFv or VH[]targeting domains are available" (see page 1631, right column). Thus, it would have been obvious to produce an immunoconjugate with the claimed properties for treating diseases associated with cancer as evidenced by the teachings of Thorpe et al, Berkner et al, and Wang et al. Therefore, claims 1-20 lack an inventive step under PCT Article 33(3) as being obvious over Thorpe et al. in view of Berkner et al. and Wang.

The response filed 26 July 2001 as paper #4 has been carefully considered but is deemed not to be persuasive. The response states Thorpe et al's molecules are different that applicants in that applicants conjugates are composed of factor VII and an FC region of an immunoglobulin. In response to this argument, Thorpe et al teach the bispecific agents can be fusion proteins prepared by cDNA encoding a binding ligand and a cDNA encoding a coagulation factor (see column 9, lines 48-63) and the coagulation factor can be factor VII and can contain modifications. The response also argues the references individually when the report is based on the combination of references.

----- NEW CITATIONS -----

NONE

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/02439 A1

- (51) International Patent Classification⁷: C07K 16/00, A61K 39/395
- (21) International Application Number: PCT/US00/16481
- (22) International Filing Date: 14 June 2000 (14.06.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/142,161 1 July 1999 (01.07.1999) US
- (71) Applicant (*for all designated States except US*): YALE UNIVERSITY [US/US]; Office of Cooperative Research, 155 Whitney Avenue, New Haven, CT 06520-8336 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (*for US only*): GAREN, Alan [US/US]; 278 Canner Street, New Haven, CT 06511 (US).
- (74) Agent: KRINSKY, Mary, M.; 79 Trumbull Street, New Haven, CT 06511-3708 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— *With international search report.*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 01/02439 A1

(54) Title: NEOVASCULAR-TARGETED IMMUNOCONJUGATES

(57) Abstract: Immunoconjugates for treating diseases associated with neovascularization such as cancer, rheumatoid arthritis, the exudative form of macular degeneration, and atherosclerosis are described. The immunoconjugates typically consist of the Fc region of a human IgG1 immunoglobulin including the hinge, or other effector domain or domains that can elicit, when administered to a patient, a cytolytic immune response or cytotoxic effect against a targeted cell. The effector domain is conjugated to a targeting domain which comprises a factor VII mutant that binds with high affinity and specificity to tissue factor but does not initiate blood clotting such as factor VII having a substitution of alanine for lysine-341 or of alanine for serine-344.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/16481

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07K 16/00; A61K 39/395

US CL : 530/387.1, 387.3, 424/130.1, 133.1, 134.1, 135.1, 155.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/387.1, 387.3, 424/130.1, 133.1, 134.1, 135.1, 155.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields search

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, MEDLINE, USPATFULL, WEST

search terms: Fe region, factor VII, immunoconjugate, Author search, scFv, neovascularization, cancer, mutant factor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim
X,P	HU et al. Targeting tumor vasculature endothelial cells and tumor cells for immunotherapy of human melanoma in mouse xenograft model. Proc. Natl. Acad. Sci. USA. July 1999, Vol. 96, pages 8161-8166, see entire document.	1-20
Y	US 5,879,672 A (DAVIS et al.) 09 March 1999 (09.03.99), see abstract and column 2, lines 1-10, column 3, lines 5-13, and column 13, lines 50-60.	1-6, 9-14, and 19
Y	US 5,861,374 A (BERKNER et al.) 19 January 1999 (19.01.99), see entire document.	1-6, 9-14, and 19

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or prior date and not in conflict with the application but cited to underpin the principle or theory underlying the invention	
*A	document defining the general state of the art which is not considered to be of particular relevance		
*E	earlier document published on or after the international filing date	*X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*L	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document combined with one or more other such documents, such combination being obvious to a person skilled in the art
*O	document referring to an oral disclosure, use, exhibition or other means		
*P	document published prior to the international filing date but later than the priority date claimed	*G	document member of the same patent family

Date of the actual completion of the international search

15 AUGUST 2000

Date of mailing of the international search report

18 SEP 2000

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Commissioner of Patents and Trademarks
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Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/16481

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to c.
Y	US 5,877,289 A (THORPE ET AL) 02 March 1999 (02.03.99), see entire document, especially figure 5, and column 10, lines 10-23.	1-6, 9-14, and 17-19
Y	WANG et al. Human single-chain Fv immunoconjugates targeted to a melanoma-associated chondroitin sulfate proteoglycan mediate specific lysis of human melanoma cells by natural killer cells and complement. Proc. Natl. Acad. Sci. USA. February 1999, Vol. 96, pages 1627-1632, see entire document, especially figure 1.	1-6, 9-14, and 19

PATENT COOPERATION TREATY

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 28 March 2001 (28.03.01)	
International application No. PCT/US00/16481	Applicant's or agent's file reference OCR-679B
International filing date (day/month/year) 14 June 2000 (14.06.00)	Priority date (day/month/year) 01 July 1999 (01.07.99)
Applicant GAREN, Alan	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 08 January 2001 (08.01.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Ant nia Müller Telephone No.: (41-22) 338.83.38
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